Remarks

Claims 1-3, 5 and 7 are currently pending. Claim 1 has been amended to overcome the written description and enablement requirements of 35 U.S.C. §112, first paragraph. The rejections under 35 U.S.C. §§103(a) and 102 are traversed, as described below.

Written Description

Claim 1 and dependent claims 3-5 are rejected under the written description requirement. The bases for this rejection appear to be:

1) the term "complementary" encompasses means of complementarity not adequately described in the specification;
2) the terms "a region of" and a "portion of" are not sufficiently described in the specification and therefore could include a region or portion of, e.g., 5 nucleotides;
3) the description of several antisense oligonucleotides cannot be used to predict the full scope of antisense oligonucleotides encompassed by the claims;
4) same as (3), but adding the contention that there are at least 263 isoforms of HDAC; and
5) there is no support in the specification for the limitation "15 to about 26 nucleotides".

Claim 1 has been amended to replace that the term "complementary" with "hybridizes under physiological conditions through Watson and Crick or Hoogsteen base-pairing", which the Office Action recognizes to be "art recognized" (see page 9, line 21). Support for this amendment is found at page 19, lines 15-17. Applicants respectfully submit that this amendment overcomes this element of the written description rejection.

The interpretation of "a region of" or "a portion of" utilized in the Office action and encompassing as few as 5 nucleotides takes these terms out of context, i.e., it disregards the remaining terms of the claims. It is part of the common and general knowledge in the art that an oligonucleotides having complementarity to only 5 nucleotides of a DNA or RNA sequence will not hybridize therewith under physiological conditions and therefore cannot inhibit the expression of such DNA or RNA sequence. The minimum length of an antisense oligonucleotide complementary to a region or portion of DNA or RNA is well known to be about 13 nucleotides or more. Therefore, Applicants respectfully submit that the interpretation of these terms in claim 1 is not a reasonable interpretation, and would not be considered as such by one skilled in the art.

Claim 1 has been amended to specify that the claimed antisense oligonucleotide hybridizes under physiological conditions through Wtson-Crick or Hoogsteen base pairing to one or more (but not all) HDAC sequence selected from the group consisting of HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7 and HDAC-8. These are sequences both disclosed in the specification and recognized by those skilled in the art as distinct HDAC isoform families. (See Yang et al., submitted herewith.) The office action maintains that there are some 263 HDAC isoforms, based on a search of the GenBank database. Although minor sequence polymorphism may allow for this many HDAC sequences to appear in the database, these sequences are not recognized as distinct isoforms of HDAC. (Again, see Yang et al.) Applicants therefore respectfully submit that this amendment to claim 1 renders it adequately described in the specification and overcomes these two elements of the written description rejection.

Claim 1 has been amended to recite "from about 15 to about 26 nucleotides". Support for this amendment is found in the specification at page 22, lines 23-24. Applicants respectfully submit that these amendments and remarks overcome the presently maintained written description rejection and request that this rejection be withdrawn.

Enablement

Claim 1 is rejected under 35 U.S.C. §112, first paragraph as not being enabled by the specification. The rejection acknowledges that the specification is enabling for making oligonucleotides that are complementary to the extent that the oligonucleotides hybridize to HDAC-1 by means of Watson-Crick or Hoogsteen base pairing, and wherein the oligonucleotide inhibits one or more HDAC genes, but not all of genes encoding HDACs 1-8. (See page 8, lines 10-14.) However, the rejection maintains that the specification is not enabling to the extent that the claims encompass oligonucleotides hybridize by some other means, wherein the oligonucleotide inhibits the expression of one or more HDAC genes, but not all of HDACs 1-8 or the 263 genes described in GenBank. As noted above, claim 1 has been amended to specify Watson-Crick or Hoogsteen base paring and to specify HDACs 1-8. (see page 8, lines 14-19.) The rejection also notes that effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells. (See page 11, lines 2-3.)

However, for purposes of enablement, the need for some experimentation is permitted, as long as such experimentation is not undue. *In re Vaeck*, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Such experimentation may be considerable, provided that it is routine. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986) Moreover, such experimentation is not undue if it is normally carried out by those skilled in the field. (See MPEP, paragraph 2106V.B.2.) In the present case, the specification proves that HDACs 1-8 can be inhibited by antisense oligonucleotides complementary to any one of HDACs 1-8. (See Table 1 on page 23 and Example 1 on pp. 33-34.) Once armed with this disclosure, one skilled in the art would merely have to resort to routine experimentation to identify additional oligonucleotides encompassed by claim 1, as is normally carried out in the field of antisense oligonucleotides.

Accordingly, for the reasons set forth above, Applicants respectfully submit that amended claim 1 (and claims 3-5 and 7, dependent thereon) are enabled by the specification and request that this rejection be withdrawn.

Obviousness rejection 1: Yoshida et al., Taylor et al., Bennett et al., Baracchini et al., Cowsert, GenBank Accession No. U50079, and Applicants' admission, Specification at page 9.

Claims 1 and 3-5 are rejected as obvious over the cited disclosures. Applicants respectfully traverse this rejection.

Yoshida et al. is cited as the closest prior art. The remaining disclosures are used to support modification of Yoshida et al. to suggest the use of antisense oligonucleotides as set forth in claim 1. However, Yoshida et al. is related to a different field (small molecules) than the instant invention (antisense oligonucleotides). Moreover, one skilled in the antisense field would not resort to the guidance of Yoshida et al. to solve an antisense problem, nor would one skilled in the art of small molecules look to antisense oligonucleotides to solve their technical problem. Neither of these propositions require any speculation, as the presently maintained rejection does. It is an objective fact that no disclosure published in the antisense field subsequent to the publication of Yoshida et al. refers to this reference, and that no reference citing Yoshida et al. suggests the use of antisense oligonucleotides. Thus, rather than speculating as to whether one of ordinary skilled in the art might combine their knowledge with the teaching of Yoshida et al., we can look to what those skilled in the antisense field actually have done, which is not to look to Yoshida et al. for guidance. As discussed in Appellants' brief, Yoshida et al. addresses the technical problem that the only known HDAC small molecule inhibitor (n-butyrate) is relatively non-specific and solves that problem through the use of TSA (See Appeal Brief at pp. 3-5.) Accordingly, Applicants respectfully submit that this combination of references is improper, and request that this rejection be withdrawn. Additionally, Applicants respectfully submit that this same rejection was withdrawn in

view of the arguments made in the Appeal Brief, and that this rejection should not be reopened as a "new ground" of rejection in the current Office Action.

Obviousness rejection 2: References cited in obviousness rejection 1 in addition to newly cited Schreiber et al.

Applicants respectfully submit that this rejection is improper for the reasons discussed in obviousness rejection 1 and further for the following reasons. The current rejection essentially relies upon supposed inherent features of Schreiber et al., because Schreiber et al. merely mentions in passing antisense oligonucleotides and does not demonstrate any actual antisense oligonucleotides that inhibit HDAC-1 expression. However, this reliance upon Schreiber is misplaced. The rejection states that "that anisense oligonucleotides of Schreiber et al. function to specifically hybridize under cellular conditions with cellular mRNA or genomic DNA encoding one or more of the histone deacetylase genes so as to inhibit the expression of this gene by inhibiting transcription or translation". (See Office action at pp. 15-16) However, Schreiber et al. makes no such demonstration. Thus, this rejection relies upon supposedly inherent features of Schreiber et al. However, for purposes of obviousness, an inherent feature of a reference may be relied upon only if that inherent feature is itself obvious to one of ordinary skill in the art. *Kloster Speedsteel AB v. Crucible Inc.*, 230 USPQ 1655 (Fed. Cir. 1986). The alleged function of the antisense oligonucleotides mentioned only in passing in Schreiber et al. could not be obvious to one of ordinary skill in the art since no demonstration of antisense inhibition of HDAC-1 is made. Thus, at best, Schreiber et al. may provide a suggestion to try antisense oligonucleotides against HDAC-1, if that. It certainly does not provide the requisite expectation of success for an obviousness rejection. For these reasons, Applicants respectfully request that this rejection be withdrawn.

Novelty: Schreiber et al.

Applicants respectfully traverse this rejection because Schreiber et al. does not put the claimed invention in the possession of a person of ordinary skill in the field.

> Rejection for anticipation or lack of novelty requires as the first step in the inquiry, that all the elements of the claimed invention be described in a single reference. (Citation omitted.) Further, the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it. (Citation omitted.) *In re Spada*, 15 USPQ2d 1655 (Fed. Cir. 1990).

Unlike the present application, with its working examples, Schreiber's mere mention of an undefined antisense oligonucleotide, with no working example, does not meet the criteria of *In re Spada*. Schreiber makes no showing of any antisense oligonucleotide that actually inhibits HDAC-1 expression, let alone describing an antisense oligonucleotide that inhibits one or more, but less than all HDAC isoforms selected from the group consisting of HDACs-1-8. Accordingly, Schreiber et al. does not anticipate claim 1 or its dependent claims. Withdrawal of this rejection is respectfully requested.

It is believed that all of the objections and rejections raised in the outstanding Office Action have been addressed, and the amendments and remarks provided herewith have resolved all out-standing issues in the prosecution of the captioned application. If the Examiner believes that any discussion of this communication would be helpful, the Examiner is invited to call the undersigned attorney at 781-933-6630. Applicants respectfully request allowance of the currently pending claims.

Please charge any additional fees or credit any overpayment associated with this matter to our Deposit Account No. 50-2285.

Respectfully submitted,

Dated: October 27, 2005

Wayne A. Keown, Ph.D.
Registration No. 33,923
Attorney for Applicants

Keown & Associates
500 West Cummings Park
Suite 1200
Woburn, MA 01801
781-938-1805